improved understanding of the need to control plasma cholesterol levels, and this information is now being translated into preventive measures that can be expected to substantially affect the future expression of CAD. The NCEP guidelines are currently being revised to accommodate the new information that has recently accumulated. This information will undoubtedly be disseminated rapidly and effectively, and appropriate campaigns to achieve this goal are needed. Studies such as that done by Walsh and colleagues are important in helping to assess the effectiveness of such campaigns. Similarly, as new therapies emerge from ongoing basic and clinical research, effective strategies to disseminate the new information need to be developed in parallel. Educating physicians and the public is a vital link in the process of improving the public health.

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Therapies Directed Against Endotoxin—Has the Time Come?

IN THE UNITED STATES alone, more than 200,000 deaths each year are attributed to sepsis and septic shock.[1] Chemotherapy, transplantation, invasive procedures, and the acquired immunodeficiency syndrome epidemic have increased the number of immunodeficient patients who are at risk for septic shock. Newer antibiotics and intensive care technologies have been helpful in the management of patients with this disease, but death rates have changed little in the past 20 years. Therefore, additional therapies are needed to prevent and treat life-threatening manifestations of septic shock. The development of new treatments, however, may depend on defining how and when this syndrome occurs and what factors influence its outcome.

Our understanding of pathophysiologic events associated with septic shock has improved in recent years, though much remains to be learned. Septic shock appears to result from complex interactions among bacterial toxins, bacterial virulence factors, host inflammatory responses, and physiologic dysfunction of multiple host organ systems.[2] Some of these interactions are not detrimental to the patient, but rather protect the patient against bacterial invasion and ultimately prevent severe organ injury and death. Given the complexity of this syndrome, pharmaceutic companies should be commended for investing in therapies that might improve mortality or decrease the incidence of sepsis. The enthusiasm that welcomes these therapies, however, should not prevent a critical analysis of all in vitro, animal, and clinical studies. In this issue of THE WESTERN JOURNAL OF MEDICINE, Fang presents a timely review of the use of monoclonal antibodies against endotoxin, an investigational therapy for gram-negative sepsis.[3]

The concept that therapies directed against endotoxin, a constituent of gram-negative bacteria, might protect against morbidity from gram-negative infection is the consequence of more than 60 years of research. Fang provides an extensive review of studies examining the ability of the administration of endotoxin to mediate many of the pathophysiologic events of sepsis. In animals and humans, administering endotoxin produces organ dysfunction and cytokine release like those associated with bacterial sepsis.[4] These data suggest that endotoxin may be a fundamental mediator of septic shock and that antiendotoxin therapies might improve the outcome of this syndrome. Fang counterbalances this enthusiasm with data from the use of gram-positive bacteria that show that these pathophysiologic events can occur without endotoxin or endotoxemia.[5] Thus, the presence of endotoxin is sufficient, but not necessary, to produce septic shock. These results also suggest that antiendotoxin therapies would not be beneficial in all cases of septic shock.

Fang discusses the study of Danner and co-workers, who measured circulating endotoxin levels in patients with septic shock to determine whether endotoxemia correlated with the clinical results.[6] As stated in the review, results showed that endotoxemia was present in 43% of patients with septic shock and when present was associated with more severe manifestations of the disease. An additional finding of this study, however, was that the quantitative level of endotoxemia did not correlate with measures of severity of illness. Thus, endotoxemia was a marker of severe septic shock, but its level did not predict outcome. This finding raises some doubt as to whether a therapy that reduces the circulating level of endotoxin would be able to improve the outcome for patients with septic shock.

Despite the uncertain relationship between endotoxin levels and pathophysiologic events in septic shock, endotoxin-directed antibody therapy has been enthusiastically pursued by several investigators over the past two decades. Antibody therapies have been directed at the phylogenetically conserved inner core region of endotoxin, because these antibodies may cross-protect against diverse gram-negative bacteria. One such antibody, E5, a murine immunoglobulin (Ig) M monoclonal antibody, was found to prevent the effects of endotoxin challenge in

sheep and to protect mice administered live bacteria. Subsequently, in a large placebo-controlled trial of patients with signs of gram-negative sepsis, administering E5 did not affect the overall mortality but increased survival in a retrospectively defined subgroup of patients without refractory shock.[7] A second large clinical trial of the use of E5 failed to confirm the results of the first trial, although complete results of this second clinical trial have not yet been published.

Another antibody, HA-1A, a human IgM monoclonal antibody, was initially reported to bind to endotoxin and various gram-negative bacteria. Initial studies showed that administering HA-1A protected rabbits against the endotoxin-induced dermal Shwartzman reaction and increased the survival of mice given lethal doses of gram-negative bacteremia. After these preclinical studies, the use of HA-1A underwent a large, randomized, placebo-controlled trial in patients with presumed gram-negative sepsis. Like that with E5, HA-1A therapy did not affect the overall survival rate, but, based on a revised analytic plan, investigators reported that its use improved the 28-day survival rate in the subgroup of patients with gram-negative bacteremia and shock. United States Food and Drug Administration reviewers rejected this revised plan when they discovered that the original plan had been amended after interim results had been examined.[8] The revision contained the 28-day time point for survival analysis, which was not part of the original plan. Analysis of the study according to the original prospective analytic plan showed no notable effect of HA-1A use on survival. Therefore, the therapeutic efficacy of HA-1A has not yet been proved. A second large, multicenter clinical trial of HA-1A therapy in sepsis is currently under way.

Since the results of the HA-1A trial were published, many controversies have emerged about data from preclinical studies of this agent. Some investigators have reported that HA-1A binds to a wide variety of antigens, gram-positive bacteria, fungi, lipids, and constituents of endothelial cells.[9] Others have been unable to reproduce studies showing a protective effect of HA-1A in animals.[10] Moreover, in a recent investigation using a canine model of gram-negative septic shock, we found that administering HA-1A actually increased mortality.[11] In this randomized, blind, placebo-controlled trial, dogs were infected with an intraperitoneal clot containing *Escherichia coli* and treated with cardiovascular support, antibiotics, and either HA-1A or placebo (a control human IgM or human serum albumin). We found that the use of HA-1A (compared with placebo) was associated with a more severe form of septic shock syndrome, manifested by a worsened hemodynamic state and worsened organ dysfunction. In addition, administering HA-1A did not alter endotoxemia or bacteremia. These results suggest that its use has the potential to produce harmful effects in animals with gram-negative septic shock.

Scientists at Centocor, Inc (Malvern, Pa), the manufacturer of HA-1A, have attempted to explain the difficulty in reproducing results from murine and rabbit studies of HA-1A. Their data suggest that HA-1A binds to endotoxin and fixes complement, that HA-1A–endotoxin-complement complexes are cleared from the circulation by binding to complement receptor 1, and that these complexes are cleared through erythrocytes.[12] Because complement 1 receptors are present on the erythrocytes only of humans and nonhuman primates, the implication is that relevant studies of HA-1A can be done only in primates. Not all nonprimate studies of HA-1A have shown a lack of effect, however; specifically, our canine study showed a harmful effect. Even if the complement 1-receptor mechanism for HA-1A were validated, the possibility cannot be excluded that the effects of HA-1A seen in septic dogs might also apply to some human infections.

There is at this time no scientific proof that mandates the use of any therapy directed against endotoxin in human septic shock. Antibodies against the core region of endotoxin have not demonstrated significant survival benefit in several large multicenter clinical trials.[7,13,14] These circumstances demonstrate that our basic understanding of new therapeutic opportunities in septic shock is still incomplete. The question of whether endotoxin is truly an appropriate target for the treatment of gram-negative septic shock remains unresolved.

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